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ROLE OF THIAMINE AND ITS MOIETIES IN GROWTH RATE OF DIATOM SP. NOCICEPTIVE PAIN: CURRENT UPDATES IN MECHANISMS AND PATHWAY.

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ABSTRACT

Pain is a fundamental experience with a complex and multilayered neurobiological basis. The sensation of pain alerts us to real or impending injury and triggers appropriate protective responses. Unfortunately, pain often outlives its usefulness as a warning system and instead becomes chronic and debilitating. Pain is usually elicited by the activation of specific nociceptors (`nociceptive pain'). However, it may also result from injury to sensory fibres, or from damage to the CNS itself (`neuropathic pain'). In recent years a powerful battery of techniques has been brought to bear to unravel the mechanisms by which painful stimuli are transduced and processed. There have been several recent discoveries regarding the molecular transduction mechanisms in nociceptors and novel molecular and cellular mechanisms underlying the spinal processing of painful stimuli. The highly disagreeable sensation of pain results from an extraordinarily complex and interactive series of mechanisms integrated at all levels of the neuroaxis, from the periphery, via the dorsal horn to higher cerebral structures. In addition to familiar inflammatory mediators, such as prostaglandins and bradykinin, potentially-important, pronociceptive roles have been proposed for a variety of `exotic' species, including protons, ATP, cytokines, neurotrophins (growth factors) and nitric oxide. Further, both in the periphery and in the CNS, non-neuronal glial and immunecompetent cells have been shown to play a modulatory role in the response to inflammation and injury, and in processes modifying nociception. . In the dorsal horn of the spinal cord, wherein the primary processing of nociceptive information occurs, N-methyl-D-aspartate receptors are activated by glutamate released from nocisponsive afferent fibres. Their activation plays a key role in the induction of neuronal sensitization, a process underlying prolonged painful states. In addition, upon peripheral nerve injury, a reduction of inhibitory interneurone tone in the dorsal horn exacerbates sensitized states and further enhance nociception. As concerns the transfer of nociceptive information to the brain, several pathways other than the classical spinothalamic tract are of importance: for example, the postsynaptic dorsal column pathway. The rich variety of key molecular players that have emerged in physiological and pathophysiological pain states reflects the sophistication and uniqueness of this vitally important sense.

KEY WORDS

Nociceptive Pain, Dorsal Horn, Mediators,Sensitization.

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[1].**O**ver one-third of the world's population suffers from persistent or recurrent pain, costing the American public alone approximately $100 billion each year in health care, compensation, and litigation[2]. Nociceptive information reaches the brain from the peripheral site of injury through multiple parallel neuronal pathways[3,4]. At every stage of the pain pathway — from sensory nerve to spinal cord, from spinal cord to brainstem and from brainstem to the forebrain — information signaling injury is subdivided or shared between these parallel systems[5,6]

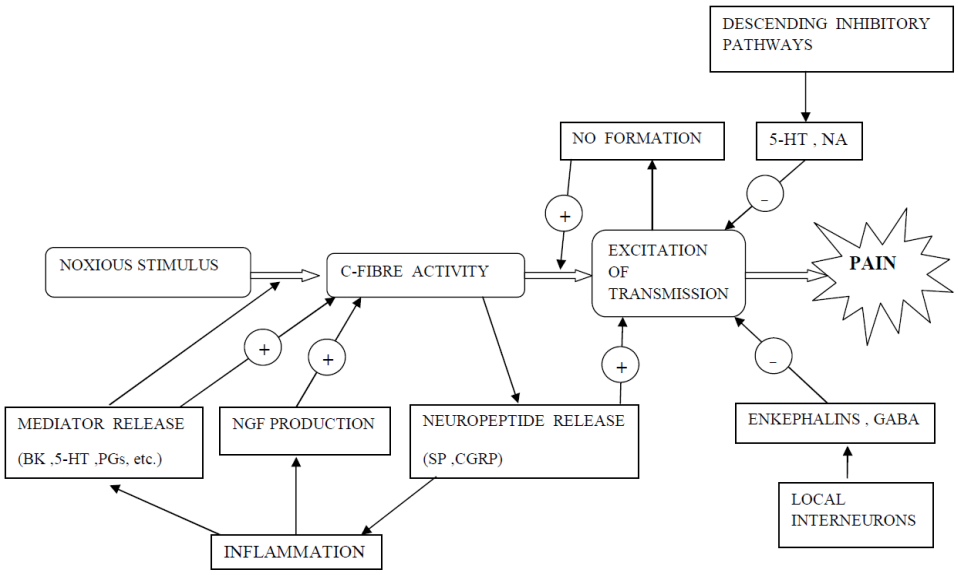

Fig1

Summary of modulatory mechanisms in the nociceptive pathway. 5-HT, 5-hydroxytryptamine; BK, bradykinin; CGRP, calcitonin gene-related peptide; NA, noradrenaline; NGF, nerve growth factor; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; SP, substance P.

Sensory fibres convey nociceptive and non-nociceptive information from the skin and most internal tissues to the spinal cord. Sensory fibres can be divided into a large number of sub-populations[7].,that in many cases respond to particular types of noxious or non-noxious stimulation.However, after damage or inflammation, the defining characteristics of these sensory neuron sub-populations, such as peptide or growth-factor receptor expression, can shift and new molecules can be expressed[8,9] Damage to sensory neurons has also revealed the presence of 'silent' nociceptors that only become active in pathological states[10,11] .Anatomically, there are two broad groups of sensory fibres:myelinated A fibres and smaller diameter, unmyelinated C fibres.Most small diameter cutaneous sensory fibres — unmyelinated C fibres and finely myelinated A fibres — are nociceptive, although ~10% of unmyelinated fibres signal only innocuous thermal information[12]. The majority of C fibres

are polymodal nociceptors and respond to all forms of noxious stimulation (thermal, mechanical and chemical), albeit with varying degrees of sensitivity[13]. Some years ago, it was proposed that polymodal nociceptors could be divided into two relatively non-overlapping groups on the basis of their content of peptides or fluoride-resistant acid phosphatase (FRAP) and their mode and site of termination within the spinal cord[14]. Remarkably, this distinction has been maintained and extended, although some peptide-containing A fibres have now been identified[15].We now know that one group of C fibres (previously identified by FRAP content) express the P2X3 purine receptor, the IB4-lectin-binding site and receptors for glial-cell-derived neurotrophic factor (GDNF). These fibres terminate almost exclusively within the deeper parts of the substantia gelatinosa of the spinal cord with a glomerular type of synaptic ending[14,16] . The other group of C fibres synthesize peptides such as substance p and calcitonin-gene-related peptide (CGRP) and express the high-affinity nerve growth factor (NGF) receptor TrkA. These fibres are largely nociceptive and terminate more superficially within the dorsal horn[17,18]. Both groups of C fibres respond to similar types of noxious stimulation and express the capsaicin VR1 receptor, which transduces noxious chemical and thermal stimulation[16,19]

Pain mechanisms and pathways :

Pain is a disabling accompaniment of many medical conditions, and pain control is one of the most important therapeutic priorities. Under normal conditions, pain is associated with impulse activity in small-diameter primary afferent fibres of peripheral nerves[20]. These nerves have sensory endings in peripheral tissues and are activated by stimuli of various kinds (mechanical, thermal, chemical;[21,22]. With many pathological conditions, tissue injury is the immediate cause of the pain and results in the local release of a variety of chemicals that act on the nerve terminals, either activating them directly or enhancing their sensitivity to other forms of stimulation.

Therefore it is useful to distinguish two components, either or both of which may be involved in pathological pain states:

- The peripheral nociceptive afferent neuron, which is activated by noxious stimuli
- The central mechanisms by which the afferent input generates a pain sensation

Cells of lamina II of the dorsal horn (the substantia gelatinosa, SG) are mainly short inhibitory interneurons projecting to lamina I and lamina V, and they regulate transmission at the first synapse of the nociceptive pathway, between the primary afferent fibres and the spinothalamic tract transmission neurons. This gatekeeper function gave rise to the term gate control theory, proposed by Wall and Melzack in 1965. According to this view, the SG cells respond both to the activity of afferent fibres entering the cord (thus allowing the arrival of impulses via one group of afferent fibres to regulate the transmission of impulses via another pathway) and to the activity of descending pathways. The SG is rich in both opioid peptides and opioid receptors, and may be an important site of action for morphine-like drugs. Elegant molecular genetic studies conducted in the past few years have now enabled us to identify specific molecules that are involved in the processes of pain transduction. A giant step forward came with the identification of proteins called vanilloid receptors, which allow us to detect noxious heat[23]. The VR1 protein is a heat transducer because it converts thermal energy into an electrical signal (action potentials) that is sent to the central nervous system, enabling us to detect a stimulus as painfully hot. Without the VR1 receptor, one does not effectively detect noxious heat, particularly in the setting of inflammation[24]. Recently, basic pain researchers have identified a number of transduction molecules that will clearly be key targets in developing pioneering pain therapies[25]

Neuronal plasticity

Plasticity is a term used to refer to changes that occur in the established nervous system.

Changes in neuronal structure; connections between neurons; and alterations in the quantity and properties of neurotransmitters, receptors, and ion channels can ultimately result in increased functional activity of neurons in the pain pathway. Conversely, plasticity can decrease the body's own pain inhibitory systems, resulting ultimately in increased pain. Injury, inflammation, and disease can all cause neuronal plasticity and increased pain by means of increased excitatory or decreased inhibitory mechanisms. Plasticity can result in short-term changes that last minutes to hours, or long-term changes which may be permanent.

Spinal cord stimulation :

Spinal cord stimulation (SCS) emerged as a direct clinical spinoff from the gate control Theory[26] Paradoxically, and in contrast to predictions from the Gate Theory, SCS proved inefficacious in acute nociceptive pain conditions, and neuropathic pain of peripheral origin eventually emerged as the cardinal indication for this mode of treatment[27,28,29,30].

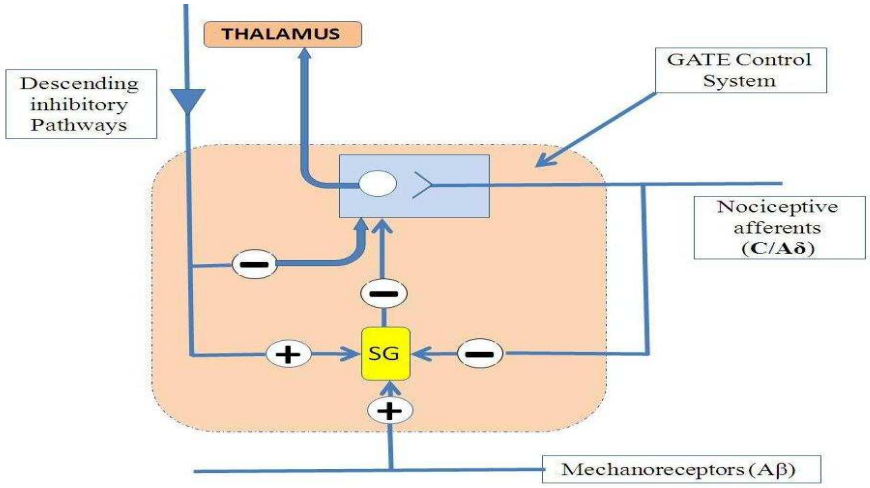

Fig 2

Schematic diagram of the gate control system. This system regulates the passage of impulses from the peripheral afferent fibres to the thalamus via transmission neurons originating in the dorsal horn. Neurons in the substantia gelatinosa (SG) of the dorsal horn act to inhibit the transmission pathway. Inhibitory interneurons are activated by descending inhibitory neurons or by non-nociceptive afferent input. They are inhibited by nociceptive C-fibre input, so the persistent C-fibre activity facilitates excitation of the transmission cells by either nociceptive or non-nociceptive inputs.

Thus, the present concepts concerning the mechanisms of pain relief with SCS differ fundamentally between the use of this therapy in neuropathic and in ischemic/vasculopathic pain conditions [28,31,32] .In neuropathic pain the hyperexcitability demonstrated by multimodal wide-dynamic range (WDR) cells in the dorsal horns[33] seems to be related to increased basal release of excitatory amino acids, e.g., glutamate, and a dysfunction of the local spinal GABA system [34,35]. SCS has, in experiments on animal models of neuropathy, been demonstrated to inhibit dorsal horn (DH) WDR hyperexcitability and to induce release of GABA in the DHs, with a subsequent decrease of the interstitial glutamate concentration[33,35]. The GABA release is solely observed in animals responding to SCS with symptom alleviation[34]. Activation of the GABA-B receptor seems to play a pivotal role for the suppression of glutamate release[35,36,37]. Available evidence indicates that stimulation-induced release of adenosine[37], serotonin and noradrenalin[31,32] (the two latter involved in descending inhibition) in the DH also may contribute.

In contrast, our own earlier studies indicated that only a minor part (<10%) of the DH inhibition is relayed by a supra-spinal

loop[38] but more recent and unpublished data point to a more important participation of the descending inhibitory tracts[39]. Another transmitter system recently found to play a major role in the effects of SCS is the cholinergic. In fact i.t. infusion of clonidine, which partly exerts its pain relieving effects via the cholinergic system, proved effective also clinically as an adjunct to SCS when stimulation alone was ineffective – another therapeutic possibility and an example of ‘‘drug-enhanced spinal stimulation”[40,41].However, a cascade release of neuroactive substances is probably induced or modulated by SCS both in the DHs and in other sites, e.g., in the brain stem[42], and multiple, as yet unknown, mechanisms thereby activated[43,44]. SCS has during the last years demonstrated its efficacy in complex regional pain syndromes (CRPS)[45,46,47,48,49,50]

Descending inhibitory systems :

It is well established that the brainstem has a significant role in regulating pain-related signals at the spinal cord level,[51,52,53,54]. It has been commonly considered that brainstem–spinal pathways predominantly inhibit pain. However, there is accumulating evidence indicating that descending pathways also have pain facilitatory effects[55,56,57,58]. Descending pain inhibitory pathways originate in or relay on a number of brainstem nuclei. Each pathway has a different neurochemistry and different neuroanatomical connections. It should be noted that some of the brainstem nuclei are involved not only in descending but also in ascending inhibition of pain-related responses[59]. Descending pain inhibitory controls are immature at birth and do not become functionally effective until postnatal day 10 in the rat[60], although all descending projections are already present at birth[61], With advanced age, the function of descending pain inhibition is impaired and this is associated with a loss of noradrenergic and serotoninergic fibers in the spinal dorsal horn[62], Conditioning noxious stimulation, which presumably activates descending pain modulatory pathways, has induced a weaker pain suppressive effect in females than in males[63] suggesting that descending inhibitory controls may have gender-specific differences. In addition to gender, other genetic differences in descending pain inhibition also exist and they may contribute to individual variability in pain sensitivity. . For example, it has been demonstrated that the descending projection and the pain inhibitory influence of the noradrenergic locus coeruleus varies with the strain of animals; i.e. locus coeruleus stimulation inhibits pain-related responses only in a strain of animals with coerulo-spinal axonal projections to the spinal dorsal horn[64]. Although the somatotopic organization of descending inhibitory influence is quite diffuse, a preferential ipsilateral antinociception induced by electrical stimulation of the midbrain periaqueductal gray (PAG) indicates that the descending inhibitory effect may not be equally distributed throughout the body[65]. A number of mechanisms are involved in mediating the descending inhibitory effect at the spinal dorsal horn level . Descending axon terminals have direct contacts with presumed pain-relay neurons of the spinal dorsal horn[66], electrical stimulation of the brainstem induced inhibitory postsynaptic potentials in nociceptive neurons of the spinal dorsal horn[67,68] and spinal application of noradrenaline, a transmitter released from descending axons, hyperpolarized a population of nociceptive spinal neurons[69] . These findings indicate that neurotransmitters released from descending axons may block the ascending pain signal by producing a hyperpolarization of spinal relay neurons (direct postsynaptic inhibition). Descending pathways may also suppress nociceptive signals due to action on central terminals of primary afferent fibers (presynaptic inhibition). Accordingly, central terminals of nociceptive primary afferents have receptors for neurotransmitters released in the spinal cord only by descending axons, such as noradrenaline[70]. Due to rareness of axo-axonic synapses between nociceptive primary afferent nerve fibers and central neurons, it has been

proposed that volume transmission may play a major role in presynaptic inhibition of nociception in the spinal dorsal horn[71]; i.e. neurotransmitter released by descending axons diffuses further away to suppress presynaptically the peripheral afferent volley in nociceptive nerve fibers . Superficial laminas of the spinal dorsal horn have a population of interneurons containing inhibitory neurotransmitters such as γ-aminobutyric acid (GABA), glycine and enkephalin[72]. Descending pathways excite some of these putative inhibitory interneurons of the spinal dorsal horn[73] and this provides one more mechanism for descending inhibition of spinal pain-relay neurons (indirect inhibition via excitation of inhibitory interneurons). Descending pain inhibitory pathways have an important role in the ascending–descending circuitry, providing negative feedback control of nociceptive signals at the spinal cord level[53]; i.e. a painful stimulus activates brainstem nuclei involved in descending antinociception and prevents excessive pain by attenuating the successive painful signals. This implies that a full activation of descending inhibition is observed only under painful conditions[74]. Similarly, mood and emotions may modulate pain through action on descending pain modulatory pathways[75]. Pathophysiological conditions may cause complex changes in descending pain regulatory circuitry. Enhanced tonic descending inhibition has been described in inflamed animals[76,77,78]. Inflammation has been associated with increased turnover of noradrenaline[79] and increased number of α2-adrenoceptors in the spinal cord[80]. These changes are likely to contribute to an increase in descending pain inhibition, and they probably explain the enhanced antinociceptive potency of spinally administered α2-adrenoceptor agonists in inflamed conditions[81,82]. However, increased efficacy of glutamatergic receptors of the medulla, accompanied by a phenotypic switch of medullary neurons, has also been observed following inflammation[83,84]. These findings indicate that plastic changes at the medullary level contribute to maintenance of enhanced descending inhibition following inflammation[85]. In contrast, phasic descending inhibition of spinal dorsal horn neurons has been reduced following a peripheral nerve injury[86,87] but not following development of diabetic neuropathy[88,89].On the other hand, peripheral nerve injury may result in compensatory upregulation of descending noradrenergic innervation to the lumbar dorsal horn[90];this upregulation of noradrenergic innervation probably explains the enhanced antinociceptive potency of spinally administered synthetic α2-adrenoceptor agonists following nerve injury[91], and in some cases it may be enough to mask neuropathic symptoms[92]. Additionally, nerve injury or inflammation may activate descending facilitation[55,56,57,93] .Following injury or inflammation, the net effect of descending controls depends on many factors such as submodality of pain, pathophysiological condition[94], time from the start of the injury[89,95], location of the test site in the injured versus uninjured area[55,58] and the brain area that is experimentally manipulated[25,96]

Recent series of studies indicating that striatal dopamine D2 receptor binding potential is associated with the occurrence of chronic orofacial pain as well as baseline pain sensitivity[97]; i.e. hypofunction of the nigrostriatal dopamine system may cause not only motor disorders but also chronic pain. Painful stimulation inhibits concurrent pain signals evoked from heterotopic stimulation sites allowing focusing of the sensory system on the most dangerous stimulus; this mechanism is called diffuse noxious inhibitory controls (DNIC)[74]. DNIC involves an opioid link and it has also been described in humans[98,99].

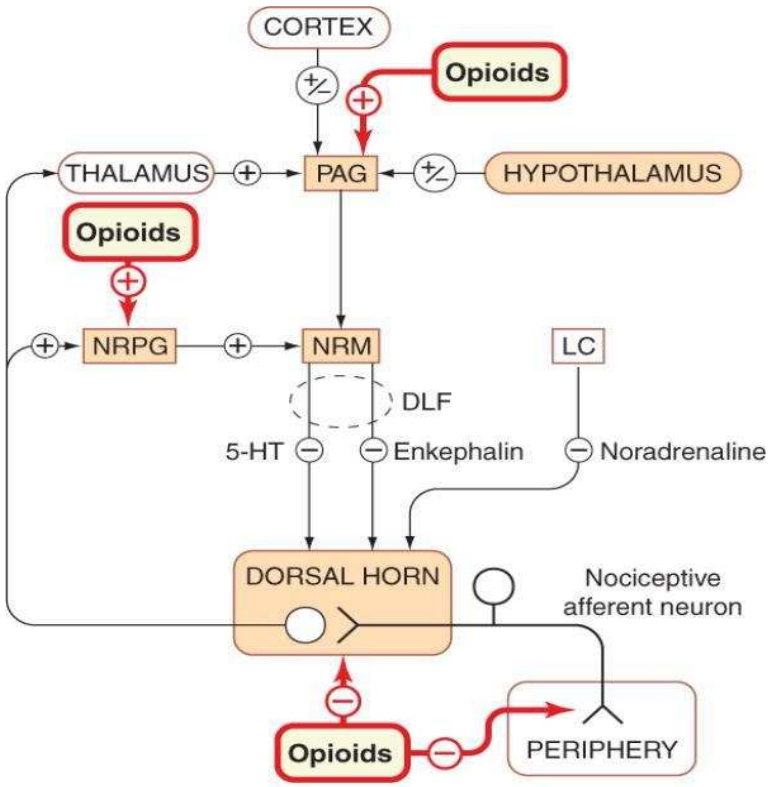

Fig 3

The descending control system, showing the main sites of action of opioids on pain transmission. Opioids excite neurons in the periaqueductal grey matter (PAG) and in the nucleus reticularis paragigantocellularis (NRPG), which in turn project to the rostroventral medulla, which includes the nucleus raphe magnus (NRM). From the NRM, 5-hydroxytryptamine (5-HT)- and enkephalin-containing neurons run to the substantia gelatinosa of the dorsal horn, and exert an inhibitory influence on transmission. Opioids also act directly on the dorsal horn, as well as on the peripheral terminals of nociceptive afferent neurons. The locus coeruleus (LC) sends noradrenergic neurons to the dorsal horn, which also inhibit transmission

Counter-irritation phenomena, including acupuncture, may, at least partly, be based on DNIC[100]. Stimulation of descending inhibitory systems has been used for treatment of various pain syndromes[101]. This treatment method is based on the fact that the amygdala–PAG–rostral ventromedial medulla (RVM)–dorsal horn endogenous antinociceptive system is endowed with high concentrations of opioid receptors in every relay station[102,103].Chronic deep brain stimulation has been used for the treatment of chronic central pain for decades but, although potentially successful, the electrical stimulation by chronic implanted electrodes of traditional pain-inhibiting centers (e.g. PAG) in humans[104] had multiple side effects[105] and therefore it was gradually abandoned. However, there are other areas that can be stimulated with success like the ventrobasal (sensory) thalamus[106], medial thalamus[107], basal ganglia[108] , periventricular gray area[109] and posterior hypothalamus[110]. A series of clinical studies reported that electrical stimulation of the motor cortex produces variable degrees of pain relief[111]. Motor cortex stimulation was effective in patients with post-stroke pain[112], phantom limb pain [113], neuropathic facial pain[114] and brachial plexus avulsion-related pain[115]

Moreover, pain treatment by some centrally acting drugs is based on enhancement of descending inhibitory controls.The PAG matter, located in the mesencephalon around the Sylvius aqueduct was the first brain area shown to exert a

powerful pain inhibitory action[116]. Both the PAG and RVM receive direct projections from the spinal dorsal horn and, thus, they may control the ascending nociceptive input by a feedback mechanism[53] . The RVM includes the nucleus raphe magnus and adjacent reticular formation, including the nucleus gigantocellularis pars and paragigantocellularis ventralis, all of which project directly to the spinal cord[117] . Based on their physiological response properties, spinally projecting RVM neurons can be classified into three types:

1) On cells that give an excitatory response to a noxious stimulus starting just prior to a spinal nocifensive reflex.
2) Off cells that give an inhibitory response to a noxious stimulus starting just prior to a spinal nocifensive reflex.
3) eutral cells that give variable responses or are unresponsive to noxious stimuli[118] .

Both on and off cells are activated by electrical stimulation of the PAG. Importantly, morphine applied systemically or in the PAG suppresses on-cell activity, increases off-cell activity and has little effect on neutral cell activity[53].Additionally, morphine administered into the RVM suppresses directly on- but not off-cell activity[119]; morphine-induced increase of off-cell activity is indirect through a GABAergic mechanism within the RVM[53]. These findings suggest that on and off cells of the RVM and supraspinal opioid receptors have an important role not only in antinociception induced by administration of morphine but also in general in descending inhibitory controls relaying through the PAG and RVM. The pain modulatory role of neutral cells of the RVM is less clear. The dorsolateral funiculus is the main descending pathway mediating antinociceptive effects from the RVM to the spinal dorsal horn[120].A number of neurochemical and neurophysiological mechanisms contribute to spinal antinociceptive effect induced by stimulation of the PAG or RVM:

(i) Among the pain inhibitory neurotransmitters are monoamines, amino acids and neuropeptides[121] ;
(ii) Among the neurophysiological inhibitory mechanisms at the spinal cord level are postsynaptic inhibition of pain-relay neurons[67],activation of inhibitory interneurons [73] and presynaptic inhibition of afferent barrage from the primary afferent nociceptive nerve fibers.

It should also be noted that the activation of the PAG–RVM–spinal cord pathway might recruit other parallel descending pain inhibitory pathways. Namely, the association of the antinociception induced by PAG stimulation with a spinal release of noradrenaline[122] and its attenuation by a spinally administered α2-adrenoceptor antagonist[123] may be explained by recruitment of a spinally projecting noradrenergic cell groups of the brainstem, such as A7 or the locus coeruleus[124,125].

A large number of brainstem, diencephalic (thalamic and hypothalamic) and telencephalic (cortical and subcortical) structures suppress pain through descending projections to the spinal dorsal horn, and in most cases their descending pain suppressive effect is relayed through the PAG and the RVM [e.g. the ventrolateral orbital cortex[126], prefrontal cortex[127], amygdala[128], parafascicular thalamic nucleus[129] and lateral hypothalamus[130]. These findings suggest that the RVM is the final relay station for descending antinociceptive action from most structures of the forebrain[131].Stressful situations like physical exercise, exposure to extreme temperatures, fight, fear and pain may induce a decrease in pain sensitivity[132,133], a phenomenon called stress induced analgesia. The hypothalamus is involved in stress-induced analgesia, since a lesion of the arcuate nucleus[134] or paraventricular nucleus[135] attenuates stress-induced analgesia, and electrical stimulation of the hypothalamus results in spinal antinociception[136]. Stress activates the hypothalamo pituitary–adrenal axis by releasing the corticotrophin releasing factor in the hypothalamus[137] and this may result in modulation of pain due to endocrine mechanisms[138]. Alternatively or in parallel,

stress may induce spinal antinociception through axonal projections from the hypothalamus to the PAG–RVM circuitry[139]. Stress-induced analgesia may be based on opioid or non-opioid mechanisms depending on several factors such as severity of the stress[140] and the body region to which stress-inducing stimulation is applied [141]. Noradrenaline is known to have a significant antinociceptive influence through action on spinal α2-adrenoceptors[142]. The source of spinal noradrenaline is descending axons originating in the noradrenergic neuronal cell groups of the brainstem[143,144], particularly the locus coeruleus (or A6) but also noradrenergic cell groups A5 and A7[145]. The locus coeruleus, A5 and A7 cell groups are connected with other pain control centers and all of them receive projections from the PAG[125]. Additionally, the locus coeruleus receives projections from the central nucleus of the amygdala, preoptic area, paraventricular nucleus of the hypothalamus and lateral hypothalamus [146]. Moreover, the descending analgesic influence triggered by PAG stimulation is partially mediated by recruitment of the descending noradrenergic system[123], through projections of the PAG and RVM to noradrenergic cell groups of the brainstem[124,143,147].

In addition to the PAG–RVM–dorsal horn circuitry and the noradrenergic nuclei of the brainstem, a large number of other brain areas from the telencephalon to the caudal medulla have been shown to inhibit pain-related responses following electrical or chemical stimulation[54]. In the brainstem, antinociceptive actions were triggered from the ventral, lateral and gigantocellular reticular nuclei, the nucleus tractus solitarius[148],caudal ventrolateral medulla[149],cuneiform nucleus[150], deep mesencephalic nucleus[151], deep layers of the superior colliculus[152], anterior pretectal nucleus[153]and posterior hypothalamic area[154].All of these areas receive afferents from[13,155] and project directly to[117,156,157] the spinal cord.

Therapeutic issues and research perspectives :

Peripheral mechanisms of opioid analgesia have gained recognition in the clinical setting. Opioid receptors have been demonstrated on peripheral terminals of sensory nerves in human synovia[158,159], dermal and epidermal nerve fibers[160] and dental pulp[161]. That such receptors mediate analgesia has been amply demonstrated in patients with various types of pain (e.g. in chronic rheumatoid arthritis and osteoarthritis, oral mucositis, bone pain, complex regional pain syndrome, after dental, laparoscopic, urinary bladder and knee surgery)[162,163,164,165,166]. Opioid peptides are found in human subcutaneous and synovial cells, mast cells, granulocytes, lymphocytes and macrophages. The predominant peptides are β-endorphin and Met-enkephalin, but dynorphin and endomorphins were also detected[167,168,169,170,171,172]. Furthermore, in patients undergoing knee surgery, blocking intraarticular opioid receptors by the local administration of naloxone resulted in significantly increased postoperative pain[171]. These findings suggest that in a stressful (e.g. postoperative) situation, opioids are tonically released in inflamed tissue and activate peripheral opioid receptors to attenuate clinical pain Apparently, endogenous immune cell-derived opioids do not interfere with exogenous agonists since intraarticular morphine is an equally potent analgesic agent in patients with and without opioid-producing inflammatory synovial cells[167,171].

These findings provide new insights into intrinsic mechanisms of pain control and open novel strategies to develop drugs and alternative approaches to the treatment of pain and inflammation. Immunocompromised patients (e.g. in AIDS, cancer, diabetes, multiple sclerosis) frequently suffer from painful neuropathies. These can be associated with intra- and perineural inflammation, with reduced intraepidermal nerve fiber density and/or with low CD4+ lymphocyte counts[173]. Thus, it may be interesting to investigate the

opioid production/release and the migration of opioid-containing leukocytes in these patients. It would be highly desirable to identify stimulating factors and strategies that selectively attract opioid-producing cells, augment opioid peptide production and/or increase peripheral opioid receptor numbers in damaged tissue. Studies using various gene therapeutic approaches are currently underway[174,175,176]. A further interesting question is whether immune-derived opioid peptides and exogenous opioids interact in a synergistic fashion. Undoubtedly, peripherally acting opioid agonists would be most attractive for their lack of central side effects (respiratory depression, nausea, dysphoria, addiction, tolerance) and their lack of the typical adverse effects of nonsteroidal anti inflammatory drugs (gastric erosions, ulcers, bleeding, diarrhea, renal toxicity, thrombo-embolic complications) in order to improve the standard of patient care in the management of acute and chronic pain.

CONCLUSION

These mechanisms which have been discussed above lead us to a beneficial conclusion that various new drugs needed to be developed which may act through various physiological mechanism to control pain.

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